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(54) Title: A REDUCED EXOTHERMIC BONE REPLACEMENT CEMENT

(57) Abstract: A bone cement having a dry component including a large constituent and a small constituent. The small constituent fills a substantial volume of the interstitial spaces between the particles of the large constituent. Therefore, only a second or minor interstitial space is left remaining between the individual particles of the small constituent and the particles of the large constituent. Therefore, a reduced amount of a polymerizable component need be added to the dry component to form a bone cement. Such a bone cement formulation decreases the exothermic temperature of the bone cement and decreases the possibility of tissue necrosis in the implantation area.

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A REDUCED EXOTHERMIC BONE REPLACEMENT CEMENT

TECHNICAL FIELD

[0001] The present invention relates to bone replacement materials, and particularly relates to reduced exothermic bone replacement materials.

BACKGROUND

[0002] The human body includes a large structural complement including a bone structure. This bone structure, however, may become damaged or need repair for various reasons. Generally, implants may be used to replace or repair damaged portions of the bone structure. One means of fixing these replacements to the bone structure is a bone cement or bone replacement. Moreover, the bone cement itself may be used as a prosthetic material.

[0003] In one example, a bone replacement may be used to reconstruct a portion of the bone structure. For example, in a cranio-facial application, the bone replacement may be molded to reconstruct a portion of the or anatomy that has been damaged due to disease, injury, congenital defect, or surgery. Therefore, the structure supporting the muscle and skin portions of the human anatomy can be replaced using the bone replacement material. Such bone replacement materials may also be used for more orthopedic applications where the bone replacement must support a load or be load bearing portion of the anatomy.

[0004] Most moldable bone replacement materials, often referred to as bone cement, include or are formed of an acrylic. In particular, the polymer of the bone cement includes a polymethylmethylacrylate (PMMA). Most often, finely divided portions of this PMMA is provided and mixed with a liquid monomer or polymerizable material such as acrylicesters. A polymerizing initiator is then added or released into the mixture and the mixture begins to polymerize and harden. For a short period of time, during the polymerization, the entire mixture is doughy or workable so that a physician may form the material into the shape and size desired for implantation and use.

[0005] The polymerization of the liquid is an exothermic reaction. Therefore, the bone cement increases in temperature or radiates heat during the polymerization process. Generally, the temperature of bone cement may increase to such a degree as to cause tissue necrosis. The necrosis can occur if the bone cement is implanted before the bone cement cools, or if the area is not cooled, such as by irrigation. This can decrease the efficiency of forming the bone cement in situ.

[0006] It has been proposed to produce an acrylic bone cement that has a large majority of large particles to form a highly porous final material. This porous bone cement allows for a large majority of bone in-growth into the porous structure. The porous bone cements require that the bone cement be formed in such a way to produce the porous product to allow bone in-growth.

[0007] Nevertheless, it is often desired to produce a non-porous bone cement while including reduced exothermic energy. That being, a bone cement that has a high strength due to the lack of pores, while still including a cool workable period so that it may be molded in situ to achieve those advantages.

SUMMARY OF THE DISCLOSURE

[0008] A bone cement that has an exothermic energy, while it is hardening, that does not create a high or substantially necrotic temperature. The exothermic energy is produced during the polymerization of the liquid that interconnects the solid or dry particles of the bone cement. The bone cement generally includes both a powder component and a liquid component which are then mixed together. The powder component may include a large particle constituent and a small particle constituent. The small constituent has an average per particle surface area and volume that is substantially smaller than the average per particle surface area or volume of the large constituent. Therefore, the small particles can fill a substantial portion of the interstitial space between the large particles. The liquid component fills the remaining interstitial space to form a substantially solid and pore free bone cement. Due to the small surface area to volume ratio of the large particles, a reduced amount of liquid component is needed to form a bone cement, thereby reducing

the amount of polymerization that must occur to form the bone cement. The reduced or limited amount of the liquid component allows the bone cement to harden without producing undo exothermic energy where substantially no or only an insignificant amount of tissue necrosis occurs.

[0009] A first embodiment provides a substantially nonporous biocompatible bone replacement formed by the combination of dry and liquid components. The bone cement includes a small particle constituent, less than 50 weight percent of a large particle constituent, and a liquid which may be polymerized. When the liquid is polymerized, it forms a polymer structure to hold the small particle constituent and the large particle constituent relative to one another.

[0010] A second embodiment provides a biocompatible bone replacement including at least 50 weight percent small particle constituent, at least 10 weight percent large particle constituent and the remainder a liquid constituent. The liquid constituent is able to polymerize after mixing with the small constituent and the large constituent. The small particle constituent, large particle constituent, and liquid constituent are able to produce an exothermic reaction energy that does not create a significant amount of necrosis of human biological tissue when mixed. The biocompatible bone replacement includes less than 5 percent pores.

[0011] A third embodiment provides a biocompatible bone replacement for implantation formed by mixing together at least 49 weight percent of a fine constituent having a first average surface area, less than 50 weight percent of a coarse constituent having a second average surface area, and the remaining portion a liquid. The liquid is able to form a polymer structure to hold the fine constituent and the coarse constituent in a selected position. The second average surface area is at least four times larger than the first average surface area.

[0012] Further areas of applicability of the present disclosure will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while

indicating various embodiment(s), are intended for purposes of illustration only and are not intended to limit the scope of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The present invention will become more fully understood from the detailed description and the accompanying drawings, wherein:

[0014] Figure 1 is a diagrammatic cross-section of a bone cement, not to scale, according to an embodiment of the formulation disclosed herein in a doughy state; and

[0015] Figure 2 is a diagrammatic cross-section of a bone cement, not to scale, according to an embodiment of the formulation disclosed herein in its hardened state.

DETAILED DESCRIPTION OF THE EMBODIMENT(S)

[0016] The following description of the embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses.

[0017] With reference to Figure 1, a bone cement 1 generally includes a dry component including a large particle or constituent 3 and a small particle or constituent 5. Defined between the large particles 3 are large interstitial spaces or voids A. Disposed within the large interstitial spaces A are the small particles 5. The small particles 5 fill a substantial volume of the large interstitial spaces A between the large particles 3. Defined between each of the small particles 5 and between the small particles 5 and the large particles 3 are small interstitial spaces B. A liquid 7 is then added to or mixed with the dry component to substantially fill the small interstitial spaces B. Before the bone cement 1 has hardened, it is in a slightly doughy or workable stage. At this point, the bone cement 1 may be molded to any desired shape before or after implantation.

[0018] The dry component 3 and 5 and the liquid component 7 are generally kept separate until an implantation time is at hand. Prior to the implantation of the bone cement 1, the dry component 3 and 5 and the liquid

component 7 are mixed. After mixing, the two components form the doughy or workable bone cement 1. The workable bone cement 1 can be worked into any number of shapes or sizes depending upon the necessities of the implantation site or procedure. During the workable time, the dry component 3 and 5 is wetted by the liquid component 7. Also, polymerization of the liquid component 7 begins. After a period of time, the polymerization nears an end and the bone cement 1 begins to harden. Once the polymerization of the liquid component 7 is complete, the bone cement is substantially hard and non-workable. At this point, the liquid component 7 has substantially polymerized therefore producing a substantially hard and complete structure, which surrounds and includes the dry component.

[0019] With reference to Figure 2, a hardened bone cement portion 10 generally includes the large constituent 3, the small constituent 5, and a polymer structure 12 formed after the polymerization of the liquid component 7. Although the illustration in Figure 2 is merely an exemplary diagram of the hardened bone cement 10, the fine constituent 5 and the polymer structure 12 substantially fills the space between the particles of the large constituent 3 to form a substantially non-porous bone cement 10. After the hardened bone cement portion 10 is formed, the fine constituent 5 substantially fills the large interstitial spaces A between the large particles 3. The polymer structure 12, which is the hardened liquid component 7, fills the small interstitial spaces B between the individual small particles 5 and between the small particles 5 and the large particles 3. Therefore, the fine constituent 5 fills or substantially fills the area between each of the individual large particles 3, the large interstitial space A. The polymer structure 12, therefore, fills only the remaining small interstitial spaces B between the individual particles of the fine constituent 5 and between the particles of the fine constituent 5 and the large constituent 3. Because of the inclusion of the fine constituent 5, the amount of a liquid component 7 necessary to form the appropriate polymer structure 12 is reduced. The polymer structure 12 substantially fills only the areas remaining between the individual fine particles 5 and between the fine particles 5 and the

large particles 3. Moreover, the hardened bone cement 10 is substantially non-porous due to the amount of fine constituent 5 and the polymer structure 12.

[0020] The dry component generally includes a divided or finely divided polymer mixture generally formed as beads of any selected geometry. The dry component according to the present formulation includes at least the large or coarse particle or constituent 3 and the small or fine particle or constituent 5. The dry component may also include other constituents such as a radiopacifier, initiator, or medicines. The initiator both initiates and is consumed in the polymerization of the liquid component 7 as it forms the polymer structure 12. Each of the dry components are held in place or held together by a polymer matrix or structure 12 formed by the polymerization of the liquid component 7.

[0021] The large constituent 3 may include both polymeric and inorganic materials. For example, the large constituent 3 may include polymer beads including PMMA. The large constituent 3 beads of PMMA may be formed in any appropriate manner, for example suspension polymerization or by comminuting large blocks of PMMA. Generally, the large constituent 3 includes a per particle size of about 200μm to about 5000μm. The per particle size is defined generally as the length of a line passing through the center of the particle connecting the two points furthest form each other on the exterior of the particle through the center. Moreover the large constituent 3 generally includes a volume of between about 1.5μl to about 1200μl. As discussed further herein, however, the size of the large constituent 3 may be selected depending upon desired properties of the doughy bone cement 1 or the hardened bone cement 10. One example includes selecting desired doughiness during the workable time and the final compressive and tensile strengths. Moreover, the large constituent 3 are generally spherical, but may also be selected depending upon desired properties of the bone cement 1, 10. The large constituents, may also be formed of inorganic materials. Suitable examples include biocompatible metals, minerals, or ceramics. Although the polymer beads may have some dissolution on the surface thereof, the relatively small amount of surface area defined by the large constituent 3 may be held in

place by the polymerized liquid component 7 substantially well if the large constituent 3 is not formed of a polymer.

[0022] The fine constituent 5 may also be formed of an appropriate polymer. For example, the fine constituent 5 may be formed of a PMMA-styrene copolymer. The fine constituent 5 generally has a per particle size of about 5μm to about 200μm. Moreover, the fine constituent has a volume of about to 0.001μl about 1.5μl. As is the case with the large constituents 3, the final size and shape of the fine constituent 5 may be selected depending upon the desired properties of the bone cement 1, 10. The fine constituent 5 may also include other additives such as a radiopacifier, one example includes barium sulfate. It will be understood that although generally many additives, not including the portions which are polymerized and formed to the actual bone cement 1,10, are within the size range of the fine constituent 5, some additives may be within the size range of the large constituent 3.

[0023] The liquid component 7 may include any substantially liquid material which can wet the dry component and be polymerized to form the polymeric structure 12 of the hardened bone cement 10. The liquid component 7 is generally polymerizable, such that it includes monomer or polymer units that may polymerize into longer chain molecules. Moreover, the polymer formed must be substantially solid when polymerized and remain so in the body. It will also be understood that the liquid component 7 may be able to dissolve and subsequently polymerize a portion of the polymer bead included either as a part of the large constituent 3 or small constituent 5. It will also be understood that the polymer may crosslink or a crosslinker may be added in the liquid component 7. An exemplary liquid includes a mixture of approximately 98% MMA monomer, about 2% di-methyl-p-toluidine, and about 60 PPM hydroquinone. This exemplary liquid component 7 has a density of about 0.94 g/ml.

[0024] The monomer of the liquid component 7 is polymerized with a polymer initiator to form the polymer matrix 12 which holds the dry component in place. Together the two components form the bone cement 10 which may be implanted into a patient at a desired location. The liquid component 7, may

be formed of other materials that are able to polymerize in the form the desired structure to produce a desirable bone cement.

[0025] As a broad overview of forming a bone cement 1, 10 and for clarity of the description, the following is provided. The dry component and liquid component 7 are generally kept separate prior to being mixed for implantation. As the dry component and liquid component 7 are mixed, the liquid component 7 wets the dry component. The liquid component 7 then begins to polymerize and form a solid polymer structure 12 that holds the dry component in place. If the dry component is formed of an appropriate polymer, a small portion of the surface area of the dry component may also dissolve and be polymerized with the liquid component 7 thereby forming a more intimate and strong interaction. Nevertheless, such a direct polymerization is not required to form the hardened bone cement 10.

[0026] As the polymerization occurs, being an exothermic reaction, the bone cement 1 begins to increase in temperature. Simply the polymerization is an exothermic reaction which produces a temperature increase of the bone cement 1. The heat is in direct proportion to the amount of polymerization occurring. Therefore, a reduction in the total amount of the liquid component 7 reduces the total amount of exothermic energy produced as the liquid component 7 polymerizes. Simply, the less material polymerizing and producing heat, the less heat that is produced. Therefore, including a smaller absolute surface area or volume which must be coated or filled by the liquid component 7, the less liquid component 7 required to form the appropriate bone cement 1, 10. Moreover, the inclusion of the small constituent 5 substantially reduces the amount of the liquid component 7 required to form the solid and substantially non-porous bone cement 10. If only the large constituent 3 were used in the dry component, the volume of the resulting interstitial spaces would be substantially greater than when the small constituent 5 is used to fill a substantial volume of the interstitial spaces between the large constituent 3. Therefore, including the small constituent 5 reduces the amount of the liquid component 7 required to form the appropriate

polymer structure 12 to form the substantially non-porous and hardened bone cement 10.

[0027] The dry component may generally include about 50 to about 90 weight percent small constituent 5 and the remainder large constituent 3. The overall volume of dry component is equivalent to previously known bone cement formulations, but may be changed depending upon the application. Including the large constituent 3 reduces the total surface area of the volume of dry component that is required to be covered by the liquid component 7 to form the polymeric matrix. It will be understood that the entire surface generally includes the combination of the surface area of the total amount of large constituents 3 and small constituents 5. As mentioned above, the small constituent 5 also fills a substantial majority of the volume between the large constituents 3. Therefore, a second theory of the formulation of the bone cement 10 is that including the small constituent 5 reduces the volume of the liquid component 7 required to fill the interstitial spaces of the dry component to form the hardened bone cement 10. Due to the reduced volume of the liquid component 7 required, the per volume exothermic energy of the workable bone cement 1 as it polymerizes to form the hardened bone cement 10 is reduced, and thus the temperature generated by the exothermic reaction is reduced. The polymerization of the liquid component 7 produces the exothermic energy per unit, therefore reducing the units of the liquid component used reduces the amount of exothermic energy produced.

[0028] The bone cement 1, 10 precursors include both the dry component and the liquid component 7. Therefore, as a weight percent of the mixed bone cement, the small constituent 5 is generally about 20 weight percent to about 80 weight percent of the bone cement precursor. The large constituent 3 is generally about 18 weight percent to about 49 weight percent of the bone cement precursor. Finally, the liquid component 7 is generally between about 5 weight percent to about 50 weight percent of the bone cement precursor. Each of these materials are mixed in appropriate proportions to form the bone cement 1, 10. Although it will be understood, as mentioned above, the specific ratios may be modified depending upon the desired

qualities of the resultant bone cement 1, 10 during its different phases. The qualities include polymerization time and workability properties and time.

[0029] Including the small constituent 5 reduces the volume of the interstitial spaces between dry components, thereby reducing the amount of the liquid component 7 required to form the bone cement 1, 10. The inclusion of an appropriate amount of the fine constituent 5 and the liquid component 7 form a substantially non-porous hardened bone cement 10. Although the bone cement 10 may have a higher porosity by including less of the fine constituent 5 and less of the liquid component 7, the substantially non-porous bone cement 10 results by filling the pores or voids between the large constituent 3 with the small constituent 5 and liquid component 7. The non-porous bone cement 10 generally has a strength which is higher than a porous bone cement of the same volume. Therefore, including at least 20 weight percent fine constituent and enough of the liquid component 7, to form the bone cement 10, produces the bone cement 10 which is substantially non-porous or less than about 5% porous. This porosity may be isolated or interconnecting. Nevertheless, porosity is generally substantially limited.

[0030] An exemplary way to form the bone cement, and to reduce porosity further, is to form it in a vacuum sealed package. Appropriate packages are disclosed in U.S. Patent No. 5,370,221 entitled "Flexible Package For Bone Cement Components" and U.S. Patent No. 5,398,483, entitled, "Method and Apparatus for Packaging, Mixing, and Delivering Bone Cement," both incorporated herein by reference. The package allows the components of the bone cement to be mixed together under a vacuum. While being mixed in the vacuum, extraneous gases are removed from the bone cement mixture as it is being mixed and the liquid component begins to polymerize. Generally, the dry component is kept separate from the liquid component 7 in a single pouch using a removable seal or clamp. The clamp is removed from the package when the two components are desired to be mixed to form the bone cement. Generally, the portion of the package which includes the dry component has been vacuum sealed such that there is substantially no gases in the interstitial spaces between the individual particles. Moreover, there is a terminal area,

having a vacuum formed therein, in gaseous communication with the portion of the package including the dry components wherein when the liquid component 7 is forced into the dry component any further gases are pulled into the terminal area. Therefore, substantially any gases in the interstitial spaces of the dry component are removed during the mixing process substantially removing any gaps between the particles. These factors help decrease the porosity of the final bone cement product 10. Therefore, using a mixing package to form the bone cement 10, may produce a bone cement 10 which is substantially highly non-porous or has a porosity below about 1%.

EXAMPLE 1: Bone Cement Precursor Formulation

[0031] An exemplary bone cement formulation includes a dry component and a liquid component. The dry component includes 60% PMMA – styrene copolymer beads (fine constituent), 10% barium sulfate (fine constituent), and 30% PMMA polymer beads (large constituent). The PMMA-styrene copolymer has an average particle size of about 65 micrometers. The PMMA polymer has an average particle size of about 750 micrometers. The liquid component of the formulation includes about 98% MMA monomer, about 2% di-methyl-p-toluidine, and about 60 PPM hydroquinone. The liquid component has a density of 0.94 grams per milliliter.

EXAMPLE 2: Bone Cement Formation

[0032] Approximately 40 grams of the dry component from Example 1 is mixed with about 14.5 milliliters of the liquid component from Example 1. The mixture is then mixed by hand and allowed to polymerize. The maximum exothermic temperature recorded of the mixture per the ASTM 451 method is about 52° C (about 120° F). The mixture reaches its dough or workability stage at about three minutes after the start of mixing. The mixture sets to its final polymerized state at about 9 minutes at about 23° C ambient temperature.

[0033] Therefore the bone cement 10, using the components disclosed herein, forms a substantially non-porous bone cement 10. That being the bone cement 10 formed generally includes a porosity less than about 5% and may be formed in a package or device to have a porosity of less than about 1%. The general lack of porosity is provided by the fact that there is

enough of the fine constituent 5 and liquid component 7 to substantially close or fill any pores that may be formed due to the large constituent 7. The fine constituent 5 and liquid component 7 fill the interstitial spaces between the large constituent 3 particles. Moreover, the bone cement 10, which has a high compressive strength and substantially non-porous structure, can be formed without producing a high exothermic temperature. Therefore, the bone cement 10 can be used in sensitive areas and need not be internally irrigated or cooled to stop tissue necrosis. In addition, surgical areas may be closed before the bone cement has fully polymerized or set thereby decreasing the surgical time required when using the bone cement.

[0034] One exemplary use of the bone cement 1, 10 is for cranio-facial bone reconstruction. One place that is exceptionally delicate includes cranial reconstruction where the bone cement may contact the dura mata. Therefore, bone necrosis or other tissue necrosis can be a substantial problem in these sensitive areas due to the fine or thin outer tissues and the fine bone structure. In these areas, it is desirable to use a substantially non-exothermic or low exothermic material for bone reconstruction in these areas. It is also highly desirable to place a workable bone cement in a surgical site for reconstructive surgery so that the formation or working of the bone cement can be done in situ to produce the most aesthetically pleasing results.

[0035] The description of the invention is merely exemplary in nature and, thus, variations that do not depart from the gist of the invention are intended to be within the scope of the invention. Such variations are not to be regarded as a departure from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A substantially nonporous biocompatible bone replacement formed by the combination of constituents, comprising:

a small particle constituent;

less than 50 weight percent of a large particle constituent; and

a liquid adapted to be polymerized;

wherein when said liquid is polymerized it forms a polymer structure to hold said small particle constituent and said large particle constituent relative one another.

2. The substantially nonporous biocompatible bone replacement of claim 1, wherein said large particle constituent includes an average particle size of at least 175 μm.

3. The substantially nonporous biocompatible bone replacement of claim 1, wherein said large particle constituent includes an average particle size of at least 200 μm.

4. The substantially nonporous biocompatible bone replacement of claim 1, wherein said large particle constituent forms about 10 weight percent to about 30 weight percent of the bone replacement; and wherein said liquid constituent forms about 10 weight percent to about 30 weight percent of the bone replacement.

5. The substantially nonporous biocompatible bone replacement of claim 1, wherein said small particle constituent and said large particle constituent are formed of a material selected from polymers or copolymers of methyl methacrylate, methylacrylate, styrene, or other esters of methacrylic acid.

6. The substantially nonporous biocompatible bone replacement of claim 1, wherein said liquid component includes a monomer, polymerization accelerator, stabilizer, or mixtures thereof, wherein when said liquid component is mixed with said large particle constituent and said small particle constituent said monomer polymerizes to form the polymer structure.

7. The substantially nonporous biocompatible bone replacement of claim 1, wherein when the polymer structure is being formed the bone replacement does not increase in temperature above 60°C as measured according to ASTM F451.

8. The substantially nonporous biocompatible bone replacement of claim 1, wherein said small particle constituent form at least 50 weight percent of the bone replacement.

9. A biocompatible bone replacement, comprising:

at least 50 weight percent small particle constituent;

at least 10 weight percent large particle constituent; and

the remainder a liquid constituent that is able to polymerize after mixing with said small constituent and said large constituent;

wherein said small particle constituent, said large particle constituent, and said liquid constituent are able to be mixed and create an exothermic reaction energy that does not create a significant amount of necrosis of human biological tissue;

wherein the biocompatible bone replacement includes less than 5 percent pores.

10. The biocompatible bone replacement of claim 9, wherein said liquid component includes a polymerizable compound, a polymerization accelerator, stabilizer, or mixtures thereof, wherein when said liquid component is mixed with said large particle constituent and said small particle constituent said polymerizable compound polymerizes to form a polymer structure.

11. The biocompatible bone replacement of claim 10, wherein when the polymer structure is being formed the bone replacement does not increase in temperature above 55° C as measured by ASTM F451.

12. The biocompatible bone replacement of claim 9, wherein said small particle constituent includes an average particle size of less than 200 μm.

13. The biocompatible bone replacement of claim 9, wherein said large particle constituent includes an average particle size of at least 500 μm.

14. The biocompatible bone replacement of claim 9, wherein said large particle constituent forms about 20 weight percent to about 30 weight percent of the bone replacement; and wherein said liquid constituent forms about 20 weight percent to about 30 weight percent of the bone replacement.

15. The biocompatible bone replacement of claim 9, wherein said large particle constituent is formed of a material selected from polymers or copolymers of methylmethylacrylate, methylacrylate, styrene, or other esters of methacrylic acid.

16. The biocompatible bone replacement of claim 9, wherein said small particle constituent includes methylmethylacrylate.

17. A biocompatible bone replacement for implantation, comprising mixing constituents together including;

at least 49 weight percent of a fine constituent having a first average surface area;

less than 50 weight percent of a coarse constituent having a second average surface area; and

the remaining portion a liquid to form a polymer structure to hold said fine constituent and said coarse constituent in a selected position upon polymerization of said liquid;

wherein said second average surface area is at least four times larger than said first average surface area.

18. The biocompatible bone replacement of claim 17, wherein said coarse constituent forms about 10 weight percent to about 30 weight percent of the bone replacement; wherein said liquid forms about 10 weight percent to about 30 weight percent of the bone replacement; and wherein said fine constituent is about 50 weight percent to about 80 weight percent.

19. The biocompatible bone replacement of claim 17, wherein said liquid component includes a monomer, a polymerization accelerator, stabilizer, or mixtures thereof, wherein when said liquid is mixed with said coarse constituent and said fine constituent said monomer polymerizes to form the polymer structure.

20. The biocompatible bone replacement of claim 17, wherein when the polymer structure is being formed the bone replacement does not increase in temperature above 65°C as measured by ASTM F451.

21. The biocompatible bone replacement of claim 17, wherein said fine constituent and said coarse constituent substantially define spheres.

22. The biocompatible bone replacement of claim 17, wherein when the polymer structure is formed, the bone replacement is less than about 5 percent porous.

23. A substantially nonporous biocompatible bone replacement formed by mixing portions comprising:

a small particle portion, wherein each small particle has a volume less than 1.5µl;

less than 50 weight percent of a large particle portion, wherein each large particle has a volume of at least 1200µl;

a liquid portion that polymerizes to hold said small particle portion and said large particle portion relative to each other.

24. The substantially nonporous biocompatible bone replacement of claim 23, wherein said large particle constituent forms about 10 weight percent to about 30 weight percent of the bone replacement; and wherein said liquid constituent forms about 10 weight percent to about 30 weight percent of the bone replacement.

25. The substantially nonporous biocompatible bone replacement of claim 1, wherein said liquid component includes a monomer that polymerizes to form a polymer structure.

26. The substantially nonporous biocompatible bone replacement of claim 1, wherein said small particle constituent form at least 50 weight percent of the bone replacement.

27. A substantially nonporous biocompatible bone replacement formed by mixing portions comprising:

less than 50 weight of a large particle defining an interstitial void;

a small particle disposed in the interstitial void to fill a first volume of said interstitial void; and

a polymer structure disposed in said interstitial void to fill a second volume of said interstitial void.

28. The substantially nonporous biocompatible bone replacement of claim 27, wherein said large particle includes an average per particle size of at least 200 μm, and wherein said small particle includes an average per particle size less than about 190 μm.

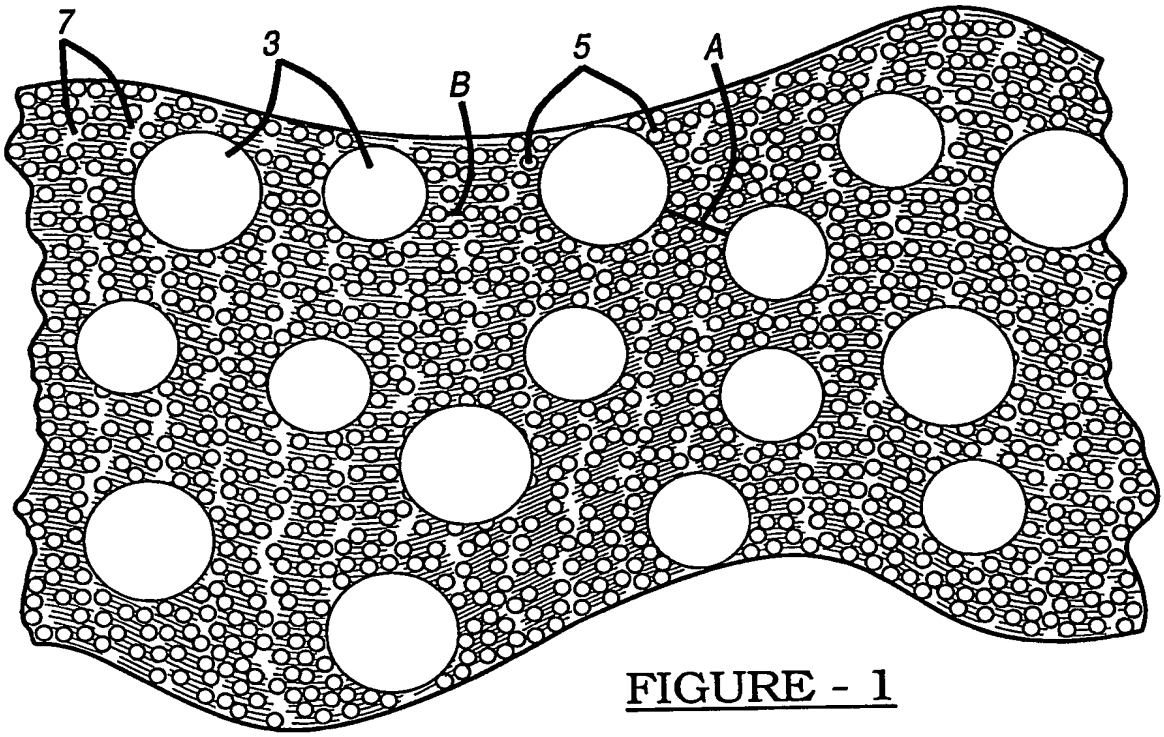

FIGURE - 1

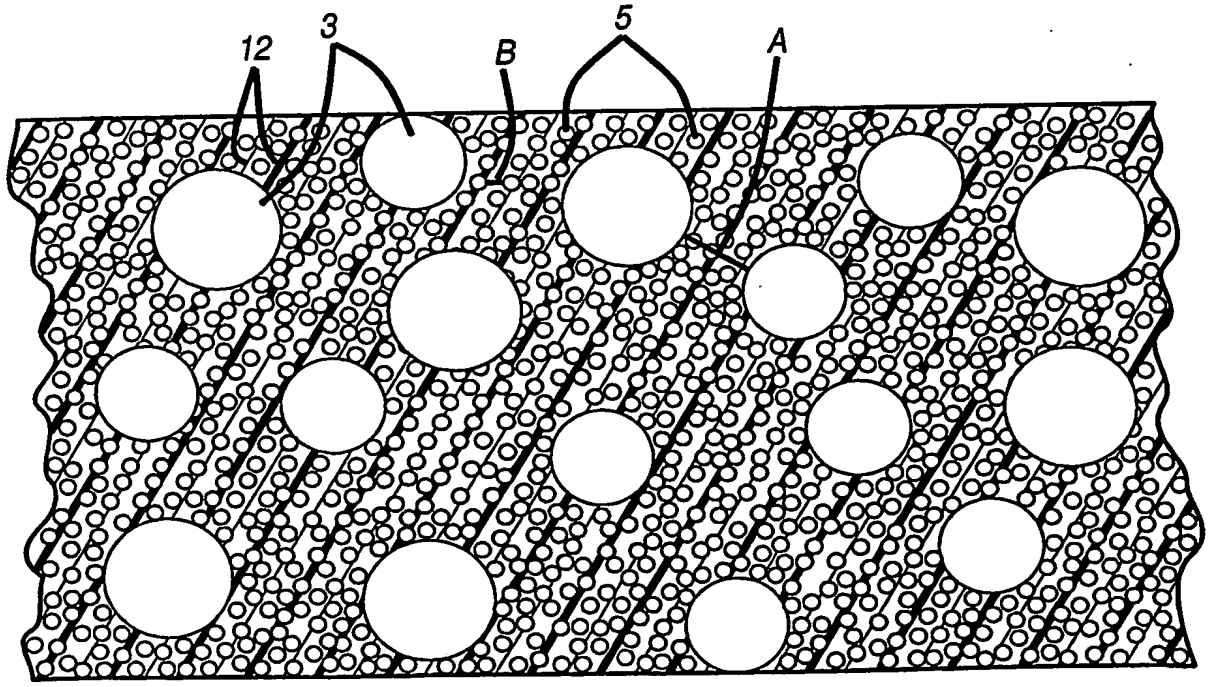

FIGURE - 2

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A REDUCED EXOTHERMIC BONE REPLACEMENT CEMENT

(57) Abstract: A bone cement having a dry component including a large constituent and a small constituent. The small constituent fills a substantial volume of the interstitial spaces between the particles of the large constituent. Therefore, only a second or minor interstitial space is left remaining between the individual particles of the small constituent and the particles of the small constituent and the particles of the large constituent. Therefore, a reduced amount of a polymerizable component need be added to the dry component to form a bone cement. Such a bone cement formulation decreases the exothermic temperature of the bone cement and decreases the possibility of tissue necrosis in the implantation area.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/26353

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 2/02; A61K 6/08, 6/083; C08K 3/30

US CL : 523/113, 115, 116; 524/423; 424/422

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 523/113, 115, 116; 524/423; 424/422

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST; bone cement, methacrylate, monomer, particle, size, granule.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,650,108 A (NIES et al) 22 July 1997 (22.06.1997), abstract, col. 3, lines 56-61, col. 4, lines 62-66, col. 5, lines 37-54 and calims 1, 4 and 15.	1-3, 5-7, 9-13, 15, 16, 23 and 25
X	US 4,373,217 A (DRAENERT) 15 February 1983 (!5.02.1983), abstract, col. 4, line 67 to col. 5, line 6 and lines 56-68.	1-4, 6, 7
X	US 4,843,112 A (GERHART et al) 27 June 1989 (27.06.1989), col. 5, lines 60-68, col. 7, lines 10-37 and col. 9, lines 17-34.	1-4, 6, 7, 9, 11-14, 17-20 and 22-28
X	US 4,837,279 A (ARROYO) 06 June 1989 (06.06.1989), col. 3, line 11 to col. 4, line 2, example 1 and claim 1.	1-7
X	US 5,795,922 A (DEMIAN et al) 18 August 1998 (18.08.1998), abstract, col. 6, lines 36-53, col. 8, line 29 to col. 9, line 16 and example 20.	1-4, 6-12, 14, 15, 17-20 and 22

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